Testicular Tumours: a Clinico-Pathological Survey

By A. JONES, M.B., D.P.H.

From the Institute of Pathology, Queen's University, Belfast

IN 1906 Clevasseau classified tumours of the testis as teratomata, seminomata, interstitial cell tumours and adenomata. He noted the similarity between the seminoma and the epithelium of the seminal tubules, and considered that this type of tumour had its origin in the seminal epithelium. Nicholson (1907), Dew (1925), and Bell (1926) were in agreement with this theory. Since then numerous publications have dealt with the diagnosis, classification, treatment and prognosis of testicular tumours. Ferguson (1933), in a large series of tumours, showed a correlation between the quantitative estimation of prolan-A in the urine, and the histological diagnosis. He found a reduction in prolan-A excretion following regression of the tumour due to radiotherapy, and a further elevation if there was a recurrence of the tumour or metastasis. He considered that a substance secreted by the tumour stimulated the pituitary to produce gonadotropin, which in turn further stimulated tumour growth. This attractive and simple, though poorly explained, theory failed to consider the work of Evans and Simpson (1929), and also of Engle in the same year. These authors demonstrated two distinct types of urinary gonadotropin in association with tumours of the testis, a chorionic gonadotropin, similar to that found in the urine of pregnancy, and a pituitary gonadotropin which exists in the urine of the normal human, but in large amounts in the castrate state. Leonard (1933) was able to confirm these findings. Further research by Jones, Gey & Gey (1943), using in vitro material, showed conclusively that cells from the human placenta, and also cells from a chorionic carcinoma, produced chorionic gonadotropin. Brewer (1946) reported two cases of testicular tumour which were diagnosed histologically, on removal, as seminoma and teratoma respectively. Both patients showed a high level of urinary chorionic gonadotropin, and at post-mortem examination both had massive metastatic deposits of chorionic carcinoma. Considering this finding, Brewer stressed the necessity to differentiate between chorionic and pituitary gonadotropin, both of which might occur in these patients.

The classification suggested by Hamburger and Neilson (1935) did not improve on that of Ferguson. These authors gave pride of place to connective tissue tumours, with little emphasis on testicular tumours proper. They tried to base their classification on the degree of radiosensitivity of the various tumours. Ewing (1911) simplified the classification by saying that all common testicular tumours originated as teratomata, the histologically uniform tumours being a unilateral development of this variety. This theory was not generally accepted. Other classifications were advanced by Friedman and Moore (1946), Anderson (1948), and Moore (1951), none of which gave any clarity to the subject.

The present trend is to classify testicular tumours as germinal or non-germinal in origin. Some workers classify all germinal tumours as teratomata. Scully and Parkam (1948) defined a teratoma as a tumour arising from a cell which had the capacity to form structures normally derived from the three germ layers, but more conservative writers prefer to see well-differentiated elements of the different germ layers before they accept the diagnosis of teratoma. Dixon and Moore (1953), in a review of 1,032 cases of testicular tumour, found that 96.5 per cent. arose from germinal epithelium. They postulated that the germ cell must be the precursor because these tumours showed a multipotentiality approaching that of the germ cell. The high incidence of germinal, or teratoid tumours, in the gonads of either sex would support this contention. These authors also found a striking similarity between the seminoma and spermatogonia. This tumour, they said, showed no transformation, either from or toward the other types of tumour. They thought that the embryonal cell carcinoma was derived from the multipotential cell, which tumour could undergo somatic or trophoblastic differentiation, and, depending on which trend was followed a teratoma or a choriocarcinoma would result. Thus, they advanced a classification as follows :—

A. Germinal	(1)	seminoma
	(2)	embryonal carcinoma
	(3)	chorion-epithelioma
	(4)	adult teratoma
B. Non-germinal	(1)	interstitial cell tumour
	(2)	any other type.

This appears to be a sound classification and it has been adopted in general detail for this review.

Methods and Material.

The records of this department, going back to 1933, were examined and a total of 85 cases of testicular tumour was found. As these were drawn from Belfast and the provinces, the actual incidence could not be estimated. Dixon and Moore (1953) stated that testicular tumours formed 1.5 to 2.0 per cent. of all malignant tumours of the male genito-urinary tract, and Scully and Parkham (1948) found that 0.562 per cent. of all cancers in males were testicular. From the 85 cases recorded, full clinical and survival data could only be obtained in 58 patients, i.e., 68.2 per cent. The age distribution and diagnosis of the cases are given in Table 1. The group incidence conforms in general detail to those reported by Kimbrought and Denslow (1951) and Willis (1953). Of the total number of tumours recorded, 85.9 per cent. are of the germinal variety, while 79.3 per cent. of the follow-up group are in this category.

Seminoma.

The typical seminoma is described as a tumour composed of large sheets of uniform round and polyhedral cells, with a distinct densely staining nucleus, and weakly eosinophilic cytoplasm. The cells may be small or large, but they are of a uniform size in each tumour. The stroma is usually fine and branching, giving the tumour a lobulated appearance, and lymphocytic infiltration may be present or absent. Frequently areas of necrosis and hæmorrhage are found (Figs. 1 and 2).

TABLE 1.

Testicular Tumours.

Type of tumour and age incidence.

Age in Follow-up Series	Seminoma	Embryonal Carcinoma	Teratoma	Chorion-Epithelioma	Miscellaneous
0- 9 - -	0	1	2	0	0
10-19 - -	0	0	2	2	1
20-29 - -	2	2	1	2	1
30-39 - -	14	2	1	2	0
40-49 - -	5	2	1	0	2
50-59 - -	2	0	1	0	6
60-69 - -	2	0	0	0	2
Other tumours in records -	12	5	2	8	0
All tumours -	37	12	10	14	12

Total—85.

Twenty-five of the followed-up group of 58 patients had produced tumours diagnosed as seminoma. In this collection there were many variants of the typical tumour. In no case was vascular or lymphatic invasion noted. Trauma has been suggested as an ætiological factor in testicular tumours, and examination of the clinical details revealed that only five gave a history of trauma. Another clinical impression is that a painful testicular tumour has a worse prognosis than has a painless one. Only six in this group gave a history of pain, two of these succumbed within 16 months, the others surviving for 4, 5, 5 and 10 years respectively, after removal of the tumour. In the clinical examinations enlarged inguinal lymph nodes were present in only one of the twenty-two cases suitable for treatment. This patient survived for five years and died of metastases. In two cases this tumour occurred in an abdominal testis, and they survived for 4 and 12 years respectively, and died of metastatic deposits. The incidence of tumours was 9 (36 per cent.) in the right and 16 (64 per cent.) in the left testis, compared with 54 per cent. and 46 per cent. recorded by Dixon and Moore (1953).

TABLE 2.

Seminomata.

Results of follow-up of 20 cases.

	Years. 0-1	-2	-4	-6	-8	-10	-12	-14	-16	Total
Dead -	3	3	1	1	0	0	1	0	0	9
Alive -	2	0	1	3	1	3	0	0	1	11

Of the 25 cases of seminoma, three presented in a moribund state, due to massive secondary deposits. Death took place before any treatment was given. These cases were confirmed at autopsy. One of the primary testicular tumours was extremely small, only being found on careful sectioning of the testis. The routine treatment was removal of the affected testis with section of the spermatic cord at the level of the internal ring. In no instance was dissection of the para-aortic lymph nodes recorded. The survival periods for 20 patients are recorded in Table 2. The three patients who died before treatment with two others who were treated but died from unrelated causes have been omitted from this analysis. The success of treatment is examined in Table 3. This shows that in the group which did not receive radiotherapy three deaths are recorded in the first year, whereas in the treated group no deaths are found in this period. Apart from favouring radiotherapy, no strong argument could be based on these figures. Before the advent

TABLE 3.

SEMINOMATA—TREATMENT AND RESULTS IN 20 CASES.

Orchidectomy with and without radiotherapy.

	YEARS									
	0-1	-2	-4	-6	-8	-10	-12	-14	-16	TOTAL
	With radiotherapy									
Dead -	0	2	1	1	0	0	1	0	0	5
Alive -	2	0	1	2	1	1	0	0	0	7
	Without radiotherapy									
Dead -	3	0	0	0	0	0	0	0	0	3
Alive -	0	1	1	0	0	2	0	0	1	5

of radiotherapy this group showed a reasonable survival level in any case. That so many cases did not receive radiotherapy and that the results in treated cases are poor is no doubt due to the fact that this survey covers a period since 1933, during most of which time radiotherapy was not so readily available, nor was it so efficient, as at present. An attempt to correlate the length of history before operation, with post-operative survival, though not conclusive, did suggest that a long history was not compatible with a good prognosis.

Teratoma.

In this survey a teratoma is accepted as a tumour showing fully developed elements of the different germ layers. In some cases this picture was complicated by the presence of other tumours, e.g., seminoma, chorion-epithelioma or embryonal carcinoma (Figs. 3 and 4). In a total of eight tumours, three were diagnosed as simple adult teratomata, and two of these patients are in good health, having survived for five and nine years. These were removed from children of 7 days and 2½ years respectively. The third specimen from a man aged 20 years, after repeated sectioning revealed no evidence of malignancy, but the patient is

recorded as dying due to metastases from a testicular tumour. It is just possible that a very small chorion-epithelioma may have existed in this teratoma which would explain the early and lethal metastases. As no autopsy was carried out, the certification of the cause of death may also be at fault. Of the remaining tumours, one appeared benign, but an area of malignancy appeared after repeated sectioning. This patient had early metastases and a short survival. Another example showed a rhabdomyosarcoma in a teratoma. He survived two years. Finally, three examples were complicated by the presence of various germinal tumours. One was a typical teratoma partly overgrown by a well-differentiated embryonal carcinoma. This patient died due to metastases ten months later. A second teratoma showed the development of a seminoma with a few areas of chorion-epithelioma. This patient has survived four months, but is receiving radiotherapy for obvious metastases. The third specimen showed overgrowth by well-developed areas of embryonal carcinoma and chorion-epithelioma. This patient received radiotherapy, but succumbed nine months after operation, due to metastatic deposits. These cases demonstrate that a teratoma may be the seat of many other types of tumour. The presence of the various germinal tumours is a point in favour of the classification and theory of Dixon and Moore (1953). In this group the value of radiotherapy is naturally dependent on the presence of complicating tumours, and the survival rate will reflect the sensitivity of these tumours to this form of treatment. Out of these eight cases, two who complained of pain had a very short survival. In no case was there a history of trauma. Right and left testes were involved equally and no correlation was shown between duration of symptoms and post-operative survival.

Embryonal carcinoma.

This type of tumour usually has a papillary, glandular structure, with fine branching stroma (Fig. 4), but it is capable of a great deal of variety and may differ very little from the atypical seminoma or chorion-epithelioma. Areas of necrosis and hæmorrhage are common. Seven tumours were classified as of the embryonal variety, and follow-up shows a survival ranging from 10 months to 8 years. The patient dying after 10 months showed obvious secondary spread at operation. Five of this group eventually died of metastases; only one of these received radiotherapy, and he survived for 8 years. Of the two remaining patients, one survived at least 2 years, but he is now untraceable, and the other is alive, with no evidence of metastases one year after operation. He has received a course of radiotherapy. In this group two showed histological invasion of blood vessels by tumour, and these had the shortest periods of survival. A history of pain was recorded in five cases, but none gave any history of trauma. That pain did not alter the prognosis is shown by the survival of two of these cases for over 5 years. Four out of seven showed involvement of the right testis, and the duration of symptoms was so irregular that no significance could be attached to it.

Chorion-epithelioma.

The typical example of this variety shows areas of syncytial cells, intermingled with sheets of epithelial-like cells, often arranged in an acinar pattern, or in large sheets (Fig. 6). This is usually a rapidly growing tumour, and frequently shows

necrosis and hæmorrhage. Six tumours were in this group, and of these five died within 8 months of operation. Only two of the five had radiotherapy, but there is no reason to believe that it was of any help in these cases. There is one survival after 3 years. He received radiotherapy after surgery, and at present is free from metastases. This patient had a history of 5 weeks' duration on first presentation, which was the shortest, the others varied up to 4 months. One patient gave a history of pain and trauma, but his prognosis was not noticeably altered by this. In the five fatal cases, obvious invasion of vascular channels was seen histologically in four. Only one chorion-epithelioma was found in the left testis and no patient had palpable inguinal lymph nodes.

Miscellaneous.

Twelve tumours were placed in this category, ten of which arose from non-testicular elements. The remaining tumours were of interest from an endocrinological point of view; these were an interstitial cell tumour, arising from the interstitial cells of the testis, while the other was believed to have arisen from an island of heterotopic adrenal tissue in the testis. These two cases, with two other non-malignant tumours survive. The remainder had a survival ranging from 2 months to 4½ years after initial surgery. As these tumours, the endocrine examples excepted, occur and behave similarly in other parts of the body, there is no indication for their further discussion. The endocrine tumours will be reported elsewhere and in more detail.

Discussion.

Relevant literature on the subject of testicular tumours underlines the difficulties in diagnosis and classification of the various types. The classification used, and the ætiological theory on which it is based, was suggested by Dixon and Moore (1953). It takes these difficulties into consideration, and goes a long way toward their solution. Most authors recognise the seminoma as a distinct entity, both ætiologically and histologically (Clevasseau, 1906; Nicholson, 1907, and others), but an anaplastic variant may easily simulate any atypical germinal tumour. This difficulty, together with the presence of germinal tumours in teratomata, induced Dixon and Moore (1953) to classify testicular tumours in combinations of tumours rather than singly.

Willis (1953) was sceptical about the possibility of two tumours arising from a single origin, and he quoted examples to show that where two tumours were found in one testis, they had distinctly separate sites of origin. He admitted, however, that some cases did not fit his explanation. The theory advanced by Dixon and Moore (1953) has already been discussed. It appears reasonable to accept that the totipotential germ cell could be the precursor of the embryonal carcinoma, chorion-epithelioma and teratoma, each tumour showing differentiation along a special line. The injection of zinc chloride into the fowl testis by Carlton, Friedman, and Bomze (1953) produced teratoid tumours. The mechanism followed was that of necrosis, then neoplastic changes in the surrounding tubules. This process took the form of a monocellular proliferation, with a pattern resembling an embryonal carcinoma, which spread as a carcinoma, underwent teratoid differentiation and ultimately showed the formation of a typical adult teratoma. The experimental

work and the presence of other germinal varieties in the examples of human teratomata described here would support the theory of Dixon and Moore (1953).

In a survey of 125 testicular tumours (Moon and Nullinghorst, 1948), interstitial cell hyperplasia was a common finding. In the cases where this was absent prognosis was improved. A similar finding in this series would have supported some personal experimental findings, and further indicate pituitary stimulation as a possible ætiological factor; but no such hyperplasia could be demonstrated. It was thought that the interstitial cells were always atrophic, and in those cases where there was a slight degree of hyperplasia it was considered that this was only apparent, following on gross tubular atrophy.

Some further observations are now compared with the findings in previously recorded series. The patients in this survey showed great age variation, from birth to 70 years old, but 60 per cent. were in the 30-50 age group. Moon and Nullinghorst (1948) found this age range to be 1½ to 53 years, with the average at 29 years. The frequency distribution of the various tumours was fairly typical, seminoma being most common, and more than equal to the sum of the other germinal tumours. The high incidence of tumours in undescended testes has been noted by Gordon-Taylor and Till (1938). Two cases, both seminomata, were found in this collection, an incidence of 3.5 per cent. which is not greatly different from that of 2.4 per cent. in the large series reported by Dixon and Moore (1953). According to Pierson (1932), bilateral testicular tumours are not rare. He quoted 46 cases from the literature and added a further example from his personal experience. No case was recorded in this series.

The history of pain in a testicular tumour has often been discussed. Leucutia, Evans, and Cook (1948) found it an unfavourable symptom. In the case histories analysed only 17 (29.3 per cent.) gave a history of pain in the affected testis, and of these one is untraceable, and five are alive, two of the latter having innocent non-germinal tumours and the other three seminomata. This finding is thus in agreement with that of Leucutia *et al.* A further question asked by the clinician when confronted with a testicular tumour is the history of trauma. This was recorded in 10 (17.4 per cent.) of the present group. It showed no correlation with the history of survival.

Treatment and Prognosis.

In the group of patients investigated the usual mode of treatment was the removal of the affected testis, with section of the spermatic cord at the level of the internal ring. In no case was a dissection of the para-aortic lymph nodes undertaken. This treatment was generally followed by radiotherapy, but in the earlier cases, the latter treatment was sometimes omitted. Lewis (1948), in a review of 250 cases of testicular tumour, thought that the treatment should vary with the pathological diagnosis, and in general this procedure has been followed here. He showed good results with surgery and radiotherapy, but did not consider the latter necessary in the absence of secondary deposits. Leucutia, Evans, and Cook (1948), in a series of 110 cases, treated by surgery and radiotherapy, were able to compare results with cases having surgery alone. They found that the combined treatment gave a much better prognosis. Gordon-Taylor and Till (1938) advocated similar

treatment. They, in conjunction with most authors, found the seminoma to be the most radiosensitive type of testicular tumour.

Lewis (1948) strongly advocated surgical removal of the tumour, with retroperitoneal dissection of the regional lymph nodes. He considered that when these were involved they were more satisfactorily treated by this method. He condemned radiotherapy in cases without obvious metastases, mainly because of the occurrence of severe reactions and some deaths in his series, when thus treated. Lowsley (1949) also found that retroperitoneal dissection of the regional lymph nodes gave a much longer survival.

The prognosis in testicular tumours generally is not good, but naturally the actual diagnosis will alter the outlook in each instance. Moon and Nullinghorst (1948) found that 50 per cent. died within 10 years of operation, and of the total deaths, 95 per cent. were in the first 2 years. Leucutia, Evans, and Cook (1948) considered that metastases present at operation need not be taken as indicative of a hopeless prognosis, as they had some reasonably long survivals in such cases. Without exception, the cases in this group, with metastases at operation, did worse than those without this complication.

TABLE 4.

ALL GERMINAL TUMOURS—TREATMENT AND RESULTS.

Orchidectomy with and without radiotherapy.

	Years									
	0-1	-2	-4	-6	-8	-10	-12	-14	-16	Total
	With radiotherapy									
Dead -	3	3	1	1	1	1	1	0	0	11
Alive -	4	1	1	3	1	0	0	0	0	10
	Without radiotherapy									
Dead -	10	2	0	2	0	1	0	0	0	15
Alive -	0	0	1	1	0	2	0	0	1	5

In Table 4 the germinal tumours are analysed with emphasis on treatment and survival. A total of 41 patients in this category was treated and followed up satisfactorily. Of these, 21 had radiotherapy post-operatively, 10 (48 per cent. approximately) of which died within 10 years, 6 (60 per cent.) being dead within 2 years. The group of 20 where no radiotherapy was given shows 15 deaths (75 per cent.) within 10 years, and 12 of these (80 per cent.) died within 2 years. It can be seen from the tabulated data that the two-year survival is 62.5 per cent. in those given radiotherapy following surgery and 40 per cent. in those not receiving this form of treatment. From these results it is reasonable to say that radiotherapy, following on surgical treatment, improves the prognosis. The highest incidence of deaths was in the first two years, which is a common and expected finding. The group without radiotherapy shows five survivals, and it is believed that these are patients who were fortunate enough to be seen before metastases had occurred.

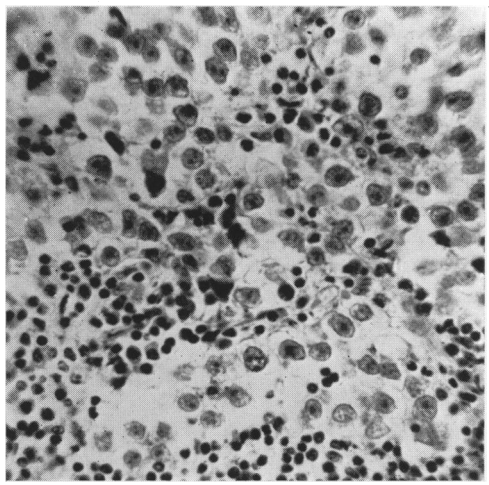

Fig. 1.
A seminoma, with dense lymphocytic infiltration of the stroma. (× 400)

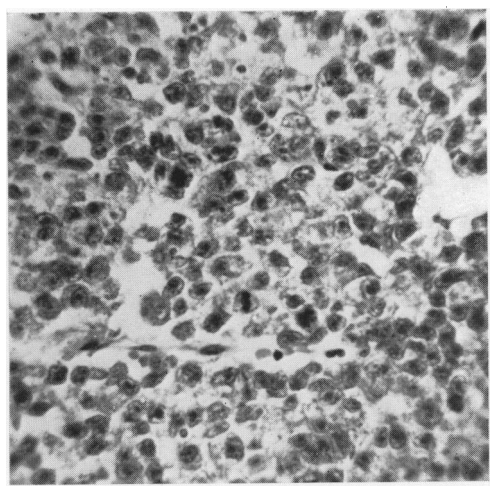

Fig. 2.
A seminoma, with numerous mitotic cells. (× 400)

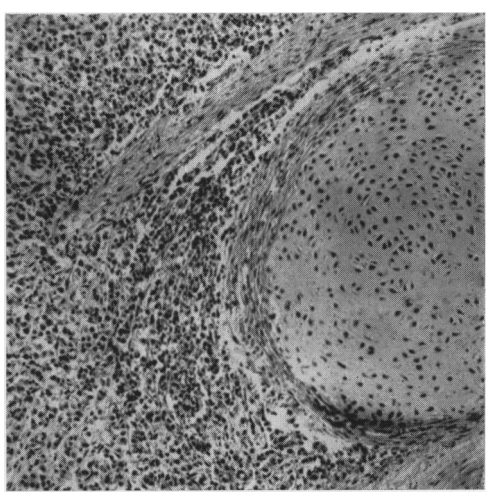

Fig. 3.
A teratoma, showing an area of cartilage and overgrowth by a seminoma. (× 80)

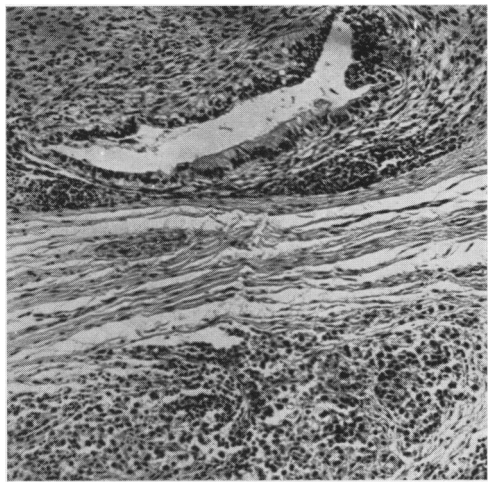

Fig. 4.

Showing another area of the tumour shown in Fig. 3. Well-formed columnar epithelium is evident. (× 80)

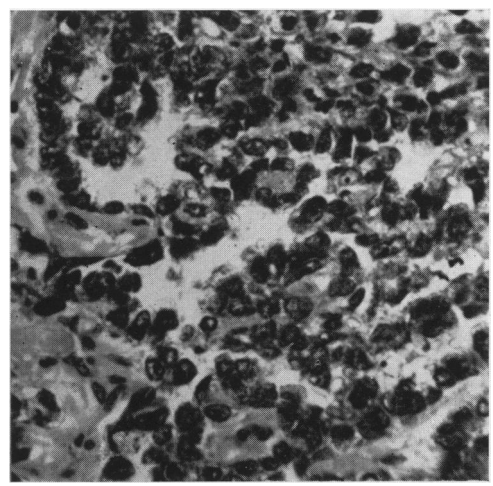

Fig. 5.

An embryonal carcinoma, showing papillary structure, with large densely staining cells. (× 400)

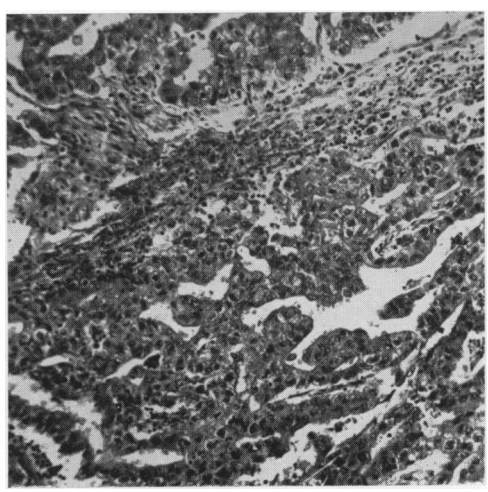

Fig. 6.

A chorion-epithelioma, showing sheets and columns of large epithelioid cells. (× 230)

TABLE 5.

FOLLOW-UP DATA FOR DIFFERENT TYPES OF GERMINAL TUMOURS.

	Seminoma	Teratoma	Embryonal Carcinoma	Chorion-Epithelioma
2 years				
Alive	12	2	4	1
Dead	6	5	2	5
4 years				
Alive	10	2	3	–
Dead	7	5	2	5
6 years				
Alive	6	1	1	–
Dead	8	5	4	–
8 years				
Alive	5	1	0	–
Dead	8	5	5	–
10 years				
Alive	2	–	–	–
Dead	8	5	–	–

This table demonstrates the incidence of survivals and deaths at two-year intervals.

Table 5 shows that in the seminomata 8 deaths (40 per cent.) occurred from metastases within 6 years, of the teratomata 80 per cent. died within 2 years, while over a similar period the chorion-epitheliomata showed 83.3 per cent., all of the latter died in less than one year after surgical treatment. The embryonal carcinoma group shows only 33.3 per cent. deaths in the two-year period.

When the total of 58 patients is considered it is found that 26 (44.8 per cent.) are known to have died, due to metastases within 10 years. Of these, 20 (77 per cent.) died in the first 2 years. These figures correspond to those of Moon and Nullinghorst (1948) and they emphasise the poor prognosis in the chorion-epithelioma and teratoma groups; the latter, no doubt, has a bad prognosis because of the frequent occurrence of elements of the former as a complication. The chorion-epithelioma is the least responsive to radiotherapy, so that early radical surgery is the best hope for survival.

It is clear that early diagnosis increases the survival rate. In the presence of metastases early and adequate radiotherapy is essential. The need to explain the importance of this treatment to the patient is emphasised by at least one patient in the series. He failed to attend for completion of his course, not realising its importance, and no doubt this contributed to his early demise. Dissection of the regional lymph nodes, in selected cases, would appear to have definite advantages. The institution of routine chest X-ray for all patients with testicular tumours is a necessity, but was often lacking in the cases analysed.

SUMMARY.

A total of 85 testicular tumours has been analysed, and a comprehensive study carried out on 58 of these, in whom an adequate clinical history and follow-up was

available. Recent views on ætiology and classification are presented. Factors which may help in prognosis, the general lines of treatment and their indications are described and discussed.

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